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Letter to the Editor

Stroke-Like Episodes in A Highly Heteroplasmic M.14487T>C Carrier Not Necessarily Imply MELAS

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In a recent article, Xu *et al.*, reported about a 58yo Chinese male who was diagnosed with MELAS upon the clinical presentation and the presence of the m.14487T>C mutation in the *ND6* gene (Xu, X. B. *et al.*, 2019). We have the following comments and concerns.

We do not agree that his patient had MELAS. Though the patient presented with features of a mitochondrial disorder (MID), a number of typical MELAS features was absent in the presented patient, including migraine-like headache, short stature, cortical blindness, basal ganglia calcification, and abnormal muscle biopsy with COX-negative, ragged-blue fibers, or ragged-red fibers (RRFs) (El-Hattab, A.W. *et al.*, 2001 Feb 27). Though stroke-like episodes (SLEs) most frequently occur in MELAS, they have been also reported in Leigh syndrome, MERRF, CPEO, KSS, LHON, SLSJCOX deficiency, POLG1-related disorders, triple-H syndrome, CoQ-deficiency, and mitochondrial multiorgan disorder syndromes (MIMODSs) [Finsterer, submitted]. SLEs may even occur in non-mitochondrial disorders. A further argument against MELAS is the late onset of the MID. According to the Hirano criteria, stroke-like episodes (SLEs) need to occur before age 40y for being diagnostic for MELAS, which was not the case in the presented patient.

The high heteroplasmy rate of 98% in the skeletal muscle suggests that the muscle should be clinically or morphologically affected. However, muscle biopsy was normal, a discrepancy which should be explained0. Particularly we should be informed if mitochondria showed any abnormalities on ultrastructural investigations of the muscle biopsy. Additionally, results of the biochemical investigations of the muscle homogenate should be presented, particularly which of the respiratory complexes showed reduced activity.

The authors argue that high heteroplasmy rates imply early onset. However, 97% heteroplasmy rate in muscle was associated with an onset at age 46y. The authors should explain this discrepancy. The authors also argue that PGD provides female carriers of an mtDNA variant "a fair chance of having healthy offspring" (Xu, X. B. *et al.*, 2019). We strongly disagree with this appreciation as there is evidence that very low heteroplasmy rates early in life may progress to higher and pathogenic heteroplasmy rates with progression of the disease (Stewart, J.B., & Chinnery, P.F. 2015).

Missing in this report is the family history. We should be informed if the mtDNA variant m.14487T>C was found in any of the first degree relatives and if any of them presented with clinical features of a MID. About three quarters of the mtDNA variants are maternally transmitted, the remained is assumed to occur sporadically (Poulton, J. *et al.*, 2017).

Since the patient had epilepsy, we also should be informed about the semiology of the seizures, their onset, their frequency, and how they responded to antiepileptic drug (AED) treatment. In particular, we should be informed if seizures occurred only in association with SLEs or also in the interval between

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the SLEs and if any mitochondrion-toxic AEDs were given. From VPA, CBZ, PHT, and PB it is well-known that they are potentially mitochondrion-toxic (Finsterer, J. 2017). Since SLEs may go along with seizures or epileptiform discharges on EEG (El-Hattab, A.W. *et al.*, 2001 Feb 27), we should be informed if the recurrent SLEs were always accompanied by epilepsy or not.

Due to the enlargement of the left atrium it is conceivable that there was atrial fibrillation in this patient. Thus, we should be informed if there were any indications for cardio-embolic events clinically or on imaging and which were the results of the long-term ECG recordings? Was the patient supplied with an event recorder?

Overall, this interesting case report could be more meaningful if detailed individual epilepsy and cardiac history and the family history were provided, if first-degree relatives were clinically and genetically investigated, and if the indicated inconsistencies were clarified.

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